

**REMARKS**

Claims 3, 4 and 27 have been canceled.

Claims 1, 2 and 5-26 are currently pending in the present application.

Claims 12-21 and 23-26 are withdrawn from consideration as being directed to a non-elected invention.

Claim 5 has been amended by deleting subsection (b).

Claim 6 has been amended by changing the dependency to include claim 5.

No new matter has been added.

**Rejections Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness**

The Examiner has rejected claim 27 as indefinite, contending that it is unclear whether claim 27 is supposed to have any relation to subpart (a) of claim 5 or if claim 27 was attempting to further limit the replicon of claim 5 subsection (b) by limiting the number of nucleotide changes permitted.

Applicants do not agree with the Examiner's allegations, but have canceled claim 27 without prejudice or disclaimer of the subject matter contained therein solely to move the application forward, thereby obviating the rejection.

**Rejections Under 35 U.S.C. § 112, First Paragraph**

The Examiner has rejected claims 5 and 27 for lack of written description. The Examiner contends that there is a lack of identification of nucleotides that must be maintained to retain the

required functions of autonomous replication and the ability to produce viral particles and an absence of an adequately representative number of species of the claimed genus.

Applicants do not agree with the Examiner's allegations concerning claim 5, but have deleted subsection (b) of claim 5, which is the basis of the Examiner's rejection without prejudice or disclaimer of the subject matter contained therein solely to move the application forward, thereby obviating the rejection.

With respect to claim 27, Applicants again do not agree with the Examiner's allegations, but have canceled claim 27 without prejudice or disclaimer of the subject matter contained therein solely to move the application forward, thereby obviating the rejection.

#### Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 1, 2, 5-11 22 and 27 as obvious over Kato et al. in view of Ikeda et al. and EMBL AB047639. The Examiner alleges that there is no evidence of uncertainty in the ability of full-length genomic replicons to replicate where the subgenomic replicon of that HCV isolate has been shown to replicate and thus the full-length replicon of HCV strain JFH-1 is an obvious functional equivalent of the subgenomic replicon disclosed in the Kato et al. reference. Applicants respectfully traverse.

The Pietschmann et al. reference (J. Virol 76:4008-4021 (2002); attached hereto) states on page 4011, left column, lines 6-30 (see "RESULTS" section):

"To allow analysis of the complete viral life cycle in vitro, we wished to establish cell lines that harbor autonomously replication full-length HCV genomes. Initially, we generated a selectable HCV genome that was based on

the original sequence of the Con1 isolate and that had an organization similar to that of the subgenomic replicons described previously (49). However, we failed to establish viable cell clones after transfection of the RNA and selection with G418 (data not shown). Therefore, after we had identified cell culture-adaptive mutations that increase HCV RNA replication dramatically, an sfl genome that carried an *Sfi*I fragment derived from the highly adapted subgenomic replicon rep 5.1 was generated (Fig. 1A) (43). In addition to the heterologous sequences introduced, the resulting HCV genome differed from the original genome by six amino acid substitutions. While three of these mutations did not affect replication, the combination of the three remaining ones synergistically increased RNA replication efficiency (E1202G and T1280I in NS3 and S2197P in NS5A) (43). Upon transfection of Huh-7 cells with this sfl genome, we were able to generate a panel of G418-resistant colonies. However, it is noteworthy that the efficiency of colony formation (ECF) per microgram of transfected RNA was about 3 to 4 orders of magnitude lower than the ECF of the respective subgenomic replicon rep 5.1.”

(emphasis added)

As shown above, Pietschmann et al. (2002) describes that an HCV full-length replicon could not necessarily be obtained using an existing HCV subgenomic replicon unless highly adaptive mutations were introduced, and then the efficiency of colony formation (i.e., the efficiency of generating a full-length genomic replicon) was very low even using the highly adapted subgenomic replicon. This is evidence that a person skilled in the art understood that the HCV

full-length replicon was not an obvious functional equivalent of an HCV subgenomic replicon. Therefore, the Kato et al. reference does not indicate that the full-length replicon of HCV strain JFH-1 was an obvious functional equivalent of the subgenomic replicon disclosed in the Kato et al. reference.

Further, the Examiner's statement “[w]hile it may be unexpected that the claimed replicons would produce viral particles, such would be inherent to the obvious use of these replicons in undergoing replication in cells for other purposes – such as screening for anti-viral drugs effective in the inhibition of viral replication of the replicon” is incorrect.

In the present invention, the full-length replicon RNA derived from the HCV JFH1 strain surprisingly enables the production of virus particles in a cell culture system. In contrast, the prior art indicates that full-length genomic replicon RNAs derived from many HCV strains could not produce virus particles in cell culture systems, and there were not reports of full-length genomic replicon RNAs capable of producing virus particles in a cell culture system. For example, Blight et al. (J. Virol. 77:3181-3190 (2003); attached hereto) states on page 3190, left column, second paragraph:

“Thus far, there is no evidence for HCV particle assembly and release from Huh-7 cells supporting replication of Con1 (3, 20) or HCV-N (10) full-length RNAs. Although Huh-7 cells may be nonpermissive for one or more of these steps, it is not known whether this will be generally true for all HCV genotypes. The well characterized H77 strain is highly infectious in chimpanzees and replicates to high titers, suggesting that it may be a good

candidate for establishing a complete replication cycle in cell culture.”  
(emphasis added)

In addition, Nature Methods 2(8):565 (2005); attached hereto) states in the third paragraph:

“Using JFH1, Wakita’s team has now made another significant breakthrough in HCV research. Working with the groups of Ralf Bartenschlager of the University of Heidelberg and T. Jake Liang at the US National Institutes of Health, they showed that Huh7 human hepatoma cells transfected with full-length JFH1 capable of producing HCV particles, could then infect new Huh7 cells (Wakita et al., 2005).”

Similar teachings are also found in many prior art reports (see, for example, Blight et al. (2002) J Virol 76:13001-13014; Pietschmann et al (2002) J. Virol 76:4008-4021 as mentioned above; EMBO report 7:14-17(2006); and even the Ikeda reference).

These disclosures indicate that the replication ability of general HCV full-length genomic replicon RNA does not necessarily provide virus particle production ability, and thus it is not inherent “to the obvious use of these replicons in undergoing replication in cells for other purposes – such as screening for anti-viral drugs effective in the inhibition of viral replication of the replicon” as stated by the Examiner.

In view of the above, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness over Kato et al. in view of Ikeda et al. Thus, Applicants respectfully request reconsideration and removal of the rejections.

Rejections for Obviousness-Type Non-Statutory Double Patenting

The Examiner has maintained his provisional rejection of claims 1-5 and 22 for non-statutory obviousness-type double patenting as being unpatentable over claims 1-13 and 21 of co-pending Application No. 10/558,155 in view of Ikeda.

The Examiner asserts that although the claims of the present invention differ from that of the cited co-pending application, since claim 5 does not require that the replicon is a full length replicon, the co-pending claims would anticipate that claim if applied as prior art. Applicants respectfully traverse.

Applicants first note that Application No. 10/558,155 discloses substantially the same invention as the Kato et al. reference. Kato et al. was used in combination with the Ikeda et al. reference as the basis for the Examiner's rejection for obviousness.

Applicants next note that, as discussed above, the instant claims are not obvious over Kato et al. in combination with Ikeda et al.

Since the instant claims are not obvious over Kato et al. in combination with Ikeda et al. and since Application No. 10/558,155 discloses substantially the same invention as Kato et al., it follows that the instant claims are not obvious over Application No. 10/558,155. Thus, Applicants respectfully request reconsideration and removal of the rejections.

Formal Request for Interview

Applicants would like to make a formal request for an Interview with the Examiner to discuss the amended claims and remarks presented in this Response in an effort to move the application to allowance. Applicants' representative will telephone the Examiner on Monday,

July 6, 2009 for a scheduling discussion. Applicants appreciate the Examiner considering this request.

Conclusion

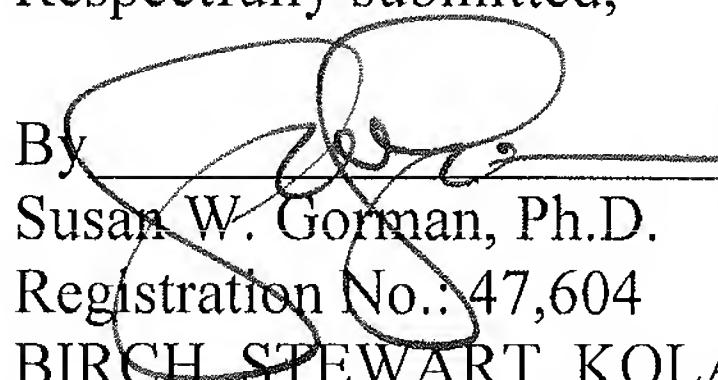
In view of the above remarks, all of the claims are submitted as defining non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Susan W. Gorman, Ph.D., Reg. No. 47,604, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Enclosures: Pietschmann et al. (2002) J. Virol. 76:4008-4021  
Blight et al. (2003) J. Virol 77:3181-3190  
Nature Methods 2(8):565 (2005)  
Blight et al. (2002) J Virol 76:13001-13014  
EMBO report 7:14-17 (2006)